REMARKS/ARGUMENTS

I. INTERVIEW

Applicants thank Examiner Gross and Examiner Epperson for phone interview on October 17, 2007, to discuss the status of the case, the outstanding rejections and proposed claim amendments. No agreement was reached during the interview. The claim amendments and arguments presented herein are consistent with the discussions during the phone interview.

II. STATUS OF THE CLAIMS

With entry of this amendment, claims 1-79, 81-84, 86-89, and 93-97 are canceled, claims 80, 85, 90-92 are amended, and claims 98 and 99 are new. Claims 80, 85, 90-92, 98 and 99 are currently pending. No new matter is added with entry of this amendment.

III. SUPPORT FOR CLAIM AMENDMENTS

Support for the claim amendments can be found throughout the specification and in the priority documents U.S. Pat. App. No. 09/526,106, filed March 15, 2000, of which the present application is a continuation-in-part, and U.S. Prov. App. No. 60/175,968, filed January 13, 2000, of which the present application claims benefit.

Specifically claim 80 is amended to clarify that the first or second interactor domain can be a member of an expression library, a member of a constrained peptide library, and a member of a thioredoxin peptide library. Support for the amendment can be found in the Pre-Grant Pub. No. 2003/0165825 at paragraph [0035] which states that "...either or both the first and second interactor domain can be a member of a library....The libraries can encode any representative synthetic or naturally occurring polypeptide of interest." In addition, page 7, paragraph [0044], second col. states that "the expression library is preferably a cDNA library, but can also be constructed from synthetic nucleotides to screen randomly generated polypeptides." Additional support is found at paragraph [0071] which discloses simplex and multiplex protein-protein interaction mapping using expressed sequence libraries. This same language supporting members of an expression library for use as an interactor domain can also be found in the priority document, Prov. App. No. 60/175,968 ('968 app.) filed January 13, 2000, at page 26,

paragraph 1. Support for a constrained peptide library can also be found in the '968 App., at page 26, paragraph 4, which states that "[C]onstrained peptide libraries displayed on the surface of a carrier or 'scaffold' protein may be used with β-lactamase interaction-dependent activation systems...." Support for thioredoxin peptide libraries can be found throughout the instant specification, for example at paragraph [0035] of the Pre-Grant Pub. No. 20030165825, which states "...a randomly generated peptide library presented in the context of thioredoxin." Similar support can also be found in the "968 app. at page 7, which states "[T]o date we have demonstrated the utility of the β-lactamase IdEA systems for monitoring interactions between and among cell-surface receptors, antibodies, and random peptide libraries displayed on the surface of a natural protein." Additional specific support for a thioredoxin peptide is found in the '968 Prov. App. at page 7, item 2 which states "...random 12-mer peptides in the active site of thioredoxin...."

During the phone interview, Applicant stated that the use of thioredoxin for the presentation of peptides in a constrained manner was well known in the art prior to the filing of the present application, and the Examiner requested that Applicant provide a reference in support of this fact. Lu *et al.* (1995) *Biotechnology* 13:366-372 (*see*, Information Disclosure Statement accompanying this response) teaches that the use of thioredoxin for presentation of peptides in a constrained manner was well known in the art at the time of filing the present application. Specifically, Lu *et al.*, teaches that:

> The active site of E. coli thioredoxin consists of a short disulfide-bonded loop protruding from the body of the protein, and is highly permissive for the insertion of a wide variety of peptide sequences. Most (85%) dodecamer peptides of random sequence inserted in this loop can be expressed as stable and soluble thioredoxin fusion proteins, with the inserted peptides lying on the surface of the protein where they are readily accessible to reagents such as proteases and antibodies.

See, Lu *et al.*, page 367, bottom of first col onto top of second col.

Claim 80 is also amended to limit the position of the break-point to the solvent exposed loop between amino acid residues Thr 195 and Ala 202, as discussed during the phone interview with Examiner Gross and Examiner Epperson. Support for a break-point within this

solvent exposed loop can be found in the '968 app. at page 9, which states "...identification of an exposed loop between two α-helices (approximately Thr 195 to Ala 202) within which the chain could be broken to produce fragments...." The same language is also found in the Pre-Grant Pub. No. 2003/0165825 at paragraph [0049].

Claim 85 is amended to further limit the break-point to between amino acid residues Glu 197 and Leu 198, which the Examiner acknowledges is supported by the application. Specifically, support for this particular break-point can be found in the '968 application at page 9, which states "...the α197 and ω198 fragments could be tethered together by a flexible linker between the native termini to produce a circular permutation." Additional support can also be found in Table VI (row 7) of the '968 application, which shows a high level of activity for this particular break-point.

Claim 90 is amended to clarify the claim language for a ligand-dependent circular permutation. Support for the amendment can be found throughout the '968 application, for example, figures 2 and 9, and at page 9, penultimate sentence which states "...an interaction occurs between heterologous domains fused to the break-point termini, or between these domains and a second polypeptide..." Support can also be found in the Pre-Grant Pub. No. 2003/0165825 at page 5, paragraph [0033], ultimate sentence which states: "[T]he first and second interactor domains can associate with each other allowing for a unimolecular bipartite molecular interaction, or can both simultaneously associate with a common ligand, allowing for a bimolecular tripartite molecular interaction."

Claim 91 is amended to recite the particular combinations for the bimolecular tripartite interaction as disclosed in Figure 11 of the instant application. Specifically, where ligand is a fusion of an antigen or an antibody to a monomer of a hetero-dimerizing helix, and the first interactor is an antigen, or an antibody, or a monomer of a hetero-dimerizing helix and the second interactor is either an antigen or a monomer of a hetero-dimerizing helix. Support for claim 91 can be found, for example, in Figure 11 of the Pre-Grant publication, as well as in figure 9 and at page 25 (bottom) of the '968 application. The amendment to claim 92, merely changes the claim dependency from claim 90 to claim 91.

Support for new claim 98 can be found throughout the specification as filed, in particular, at page 5, paragraph [0034] of the Pre-Grant Pub. No. 2003.0165825, which states "...a flexible polypeptide linker can separate the fragment domain from the interactor domain and allow for their independent folding." Support for new claim 99 can be found throughout the application as filed, in particular, at page 5, paragraph [0034] of Pre-Grant Pub No. 2003/0165825, which states "The flexible linker...can be as long as 30 amino acids...[I]t can be as short as 3 amino acids in length.."

As detailed above, the claims as amended are supported by the present application, Pre-Grant Pub. No. 2003/0165825, filed January 16, 2001, (which is a continuation in part of U.S. App. No. 09/526,106, filed March 15, 2000), and in U.S. Prov. App. No. 60/175,968, filed January 13, 2000, of which the instant application claims benefit. No new matter is added with the amendments.

IV. PRIORITY

The Examiner alleges that the date for purposes of prior-art concerning claims 80, 84-85, 87-88, and 90-97 is the actual filing date of January 16, 2001. *See*, page 3 of the Office Action. Specifically, the Examiner alleges that although the instant application is a CIP of U.S. Pat. App. No. 09/526,106, filed on March 15, 2000, and claims benefit of U.S. Prov. App. No 60/175,968, filed January 13, 2000, the early filed applications do not support the claims. To the extent that the earlier filed applications do not support the claims as presently recited, Applicants disagree.

Applicants have cancelled claims 93-97 rendering the priority issues to these claims moot. With regard to claim 80, Applicants have amended the claim to remove recitation to "scaffold peptide," and the limitation that the N-terminal and C-terminal break-points are within 10 amino acids in either direction from a junction of two amino acid residues located between alpha-helices 7 and 8, rendering the priority objection to these elements moot. The remaining priority objections relate to specific configurations for the ligand fusion protein. These issues are rendered moot in view of cancellation of claims 93-97, or in view of the claims 90 and 91 as presently amended in light of the support indicated above in Section III.

In view of the claims as presently amended, and the support as indicated above in Section III, Applicants respectfully request that, for purposes of prior art concerning the currently pending claims, the Examiner recognize the priority claim of the instant application as, U.S. Pat. App. No. 09/764,163, filed January 16, 2001, which is a CIP of U.S. Pat. App. No. 09/526,106, filed March 15, 2000, now abandoned, and claims benefit of U.S. Prov. App. No. 60/175,968, filed January 13, 2000.

V. CLAIM OBJECTIONS

The Examiner objected to claim 87 under 37 C.F.R. §1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. *See*, page 7, of the Office Action.

Applicants note that claim 87 is canceled with entry of this amendment, rendering the objection moot. In view of the cancellation of claim 87, Applicants request that the Examiner withdraw the objection.

VI. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

A. Enablement

Claims 80, 85-86, 88, and 90-97 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner acknowledges that the specification is enabling for circularly permuted β-lactamase comprising N and C interactor domains with a breakpoint between Glu 197 and Leu 198. The Examiner alleges, however, that the specification does not reasonably provide enablement for the other breakpoints set forth in claim 80. *See*, bottom of page 3 of the Office Action. To the extent that the rejection applies to the claims as presently amended, Applicants disagree.

Applicants note that claims 86, 88, and 93-97 are cancelled with entry of this amendment, rendering the rejection to these claims moot.

Claim 80 as presently amended recites a break-point between 2 amino acids within the solvent exposed loop between amino acid residues Thr 195 and Ala 202. A break-point within this loop is enabled by the specification as evidenced by the passage at paragraph

[0049] of the Pre-Grant Pub., and in the '968 Prov. App. at page 9, as discussed above in Section III. Claim 85 is amended to further limit the break-point to Glu197 and Leu 198, which the Examiner has acknowledged is supported by the specification. *See*, bottom of page 3, or the Final Office Action mailed July 17, 2007.

Claims 90-92 depend either directly or indirectly from independent claim 80, and therefore include all of the limitations of the independent claim from which they depend. Therefore, the arguments and amendment to claim 80 as discussed above are also applicable to the dependent claims.

In view of the arguments presented above, and the claims as presently amended, Applicants request that the Examiner withdraw the rejection.

B. Written Description

Claims 80, 84-85, 87-88, and 90-97 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. *See*, page 8 of the Office Action. Specifically, the Examiner alleges that claims 80 and 93 contain limitations to scaffold peptides and recite a break-point within 10 amino acids in either direction form a junction of 2 amino acid residues located between helices 7 and 8. The Examiner alleges that claims 90 and 94-97 introduced various ligands not supported by the specification. *See*, page 8 of the Office Action. To the extent that the rejection applies to the claims as amended, Applicants disagree.

Applicants note that with entry of this amendment, claims 84, 87-88, and 93-97 are cancelled, rendering the rejection to these claims moot. Furthermore, the rejection for "scaffold peptides" and a "break-point within 10 amino acids in either direction from a junction of 2 amino acid residues located between alpha helices 7 and 8," are also rendered moot in view of the claims as presently recited.

With regard to the Examiner's allegation that claim 90 has introduced various ligands not supported by the specification, Applicants disagree. Claim 90 is directed to a bimolecular molecular tripartite interaction described in the specification as filed. For example, page 5, paragraph [0033] of the Pre-Grant Pub. No. 2003/0165825 states that "[T]he first and

second interactor domains can associate with each other allowing for a unimolecular bipartite molecular interaction, or can both simultaneously associate with a common ligand" (emphasis added). This embodiment is clearly shown *e.g.*, in Figure 11, where the ligand is a fusion protein of an antigen (*e.g.* CD40) with a monomer of a hetero-dimerizing helix (*e.g.* fos or jun), or alternatively, the ligand is a fusion of an antibody (*e.g.* scFv) with a monomer of a hetero-dimerizing helix protein (*e.g.* fos or jun). These specific combinations are recited in claim 91.

In view of the arguments as presented above, and the claims as presently amended, Applicants request that the Examiner withdraw the rejection.

VII. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 80, 84-85, 87-88, 90-97 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Specifically, the Examiner alleges that the N-terminal break-point and the C-terminal break-point within 10 amino acids in either direction from a junction of 2 amino acid residues located between alpha helices 7 and 8 is vague and indefinite. To the extent that the rejection applies to the claims as amended, Applicants disagree.

Claims 84, 87-88, and 93-97 are cancelled with entry of this amendment rendering the rejection of these claims moot. Claim 80, as presently amended, no longer recites a break-point within 10 amino acids in either direction from a junction of 2 amino acid residues located between alpha helices 7 and 8, rendering the rejection moot. The argument presented above, with regard to claim 80, is also applicable to dependent claims 85, and 90-92, which depend either directly or indirectly from independent claim 80, and therefore include all of the limitations of independent claim 80.

In light of the claims as presently amended, and the arguments as presented above, Applicants request that the Examiner withdraw the rejection.

VIII. REJECTION UNDER 35 U.S.C. §102

Claims 80, 84 and 85 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Pieper *et al.* (1997) *Biochemistry* 36:8767 (IDS entry 5/5/2004). *See,* page 5, of the Office Action. In response to Applicants previous arguments submitted in the communication filed on April 16, 2007, the Examiner has maintained the rejection. First, the Examiner appears to rely on "scaffold peptide" as previously recited in claim 80. The Examiner alleges that giving the claims the broadest reasonable interpretation, "...*all* proteins, including circularly permutated varieties, such as beta lactamase set forth by Pieper *et al.* comprise peptide scaffolds fused at their respective N and C termini." *See*, page 5 of the Office Action. Second, the Examiner alleges that the break-points as taught by Pieper *et al.* are positioned between helices 7 and 8 as previously recited in claim 80. To the extent that the rejection applies to the claims as amended, Applicants traverse the rejection.

Applicants note that claim 84 is cancelled with entry of this amendment, rendering the rejection to claim 84 moot. With regard to independent claim 80, Applicants note that the language "scaffold peptide" has been removed from the claim, thereby rendering the Examiner's non-conventional view of Pieper *et al.* as having peptide scaffolds fused at the N and C-termini moot. Furthermore, Pieper *et al.* does not teach a circularly permutated beta-lactamase protein wherein a first and second interactor domain are fused to the N and C-termini at the break-point, as presently recited in claim 80. Specifically, Pieper *et al.* does not teach the fusion of an interactor domain to the newly created N and C-termini at the break-point, as recited in claim 80.

Furthermore, claim 80 as amended recites that the break-point is located within the solvent exposed loop between amino acid residues Thr 195 and Ala 202. Pieper *et al.* does not teach a break-point between Thr 195 and Ala 202, as presently claimed. Rather, Pieper *et al.* teaches three constructs each of which have break-points that lie outside of the claimed range of Thr 195 to Ala 202. *See*, Pieper *et al.* page 8770, second col.

Pieper *et al.* doe not anticipate the present invention, because Pieper *et al.* does not teach or suggest 1) an interactor domain as recited in claim 80; 2) a first and a second interactor domain *fused* to the circularly permutated β-lactamase protein *through* the N-terminal

and C-terminal *break-points* of the circularly permutated β-lactamase protein; and 3) a circularly permutated β-lactamase protein with a newly created N and C-terminal break-point located within the solvent exposed loop between amino acid residues Thr 195 and Ala 202 as presently claimed. Because Pieper *et al.* does not teach all of the elements of the invention, Pieper *et al.* cannot anticipate the invention as presently claimed.

In view of the arguments presented above, and the claims as presently amended, Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

/Robert C. Burrows/

Robert C. Burrows
Reg. No. 61,039

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
RCB:rcb
61172847 v1